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(54) Title: THERAPEUTIC PRODUCT AND ITS USE			
(57) Abstract The present invention is based on the discovery that, by employing certain, non-racemic, proportions of the respective enantiomers of tramadol, the most beneficial therapeutic index, in terms of analgesic efficacy and reduction of side effects (e.g. nausea, vomiting, dizziness, constipation, sedation and others) associated with administration of the racemate, may be achieved.			

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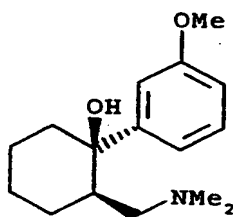
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THERAPEUTIC PRODUCT AND ITS USEField of the Invention

The present invention relates to a novel, non-racemic,
5 form of tramadol, and its use in analgesia.

Background of the Invention

Tramadol (*cis*-2-dimethylaminomethyl-1-(3-methoxy-
phenyl)-1-cyclohexanol) is a chiral drug substance which is
used as a high-potency analgesic agent. Although tramadol
10 is currently marketed as the racemate only, there has been
considerable interest in the physiological properties
associated with its individual enantiomers, namely 1*S*,2*S*-
(-)-tramadol and 1*R*,2*R*-(+)-tramadol, the latter being shown
below (1).



(1)

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In particular, the analgesic efficacy and safety of
the racemate and the individual enantiomers have been
investigated in a randomised, double-blind study with
gynaecological patients using intravenous patient-
25 controlled analgesia; see S. Grond et al, Pain (1995)
62(3):313-320. Although (+)-tramadol appeared to be more
potent in producing analgesia, it also produced more nausea
and vomiting. Since the racemate has more efficacy than
(-)-tramadol and no more side effects than (+)-tramadol,
30 the authors concluded that the racemate had more clinical
utility.

In another study it was shown that there is
complementary and synergistic antinociceptive interaction
between the individual enantiomers of tramadol; see R.B.
35 Raffa et al, J Pharmacol. Exp. Ther. (1993) 267(1): 331-
340. The enantiomers have different potencies at opioid
receptors, and in inhibiting serotonin re-uptake and

noradrenaline re-uptake. It therefore appears that both enantiomers of tramadol contribute to the analgesic effect.

Summary of the Invention

The present invention is based on the discovery that, by employing certain, non-racemic, proportions of the respective enantiomers of tramadol, the most beneficial therapeutic index, in terms of analgesic efficacy and reduction of side effects (e.g. nausea, vomiting, dizziness, constipation, sedation and others) associated with administration of the racemate, may be achieved.

According to a first aspect of the present invention a product comprises a non-racemic mixture of the single enantiomers of tramadol as a combined preparation (kit) for simultaneous, separate or sequential use in the treatment or prevention of pain.

According to a second aspect of the present invention, a non-racemic mixture of the single enantiomers of tramadol is used in the manufacture of a medicament for the treatment or prevention of pain, and is particularly useful for the treatment of patients disposed to side effects typically associated with the administration of racemic tramadol. The medicament is, however, useful in treating other patient types, as discussed below.

According to a third aspect of the claimed invention, a product comprises a non-racemic mixture of the single enantiomers of tramadol and a pharmaceutically-acceptable carrier.

Detailed Description of the Invention

In the context of the present Application, when reference is made to a non-racemic mixture of tramadol this is intended to include enantiomerically-pure (-)-tramadol, or enantiomeric excesses in respect of (-)-tramadol approaching enantiomeric purity.

Typically, the non-racemic mixture for use in the present invention comprises at least 60 wt.% (-)-tramadol. While enantiomerically-pure (-)-tramadol may be useful in achieving analgesia, it is preferred that (-)-tramadol be

formulated with at least some (+)-tramadol, as with both enantiomers present the optimal balance between analgesic efficacy and safety is achieved. Particularly preferred weight ratios of the two enantiomers lie in the range 10-40:90-60 (+)-tramadol:(-)-tramadol (+:-), more preferred ratios lie in the range 20-40:80-60 (+:-), and the most preferred ratios lie in the range 30-40:70-60 (+:-).

These preferred non-racemic mixtures are particularly useful in the treatment of patients who are disposed to side effects typically associated with the administration of racemic tramadol. A couple of examples of such side effects are given above. Other side effects typically observed in the administration of racemic tramadol include blurred vision, drowsiness, somnolence, hallucinations, respiratory depression, and euphoria. The present invention, however, is particularly useful in treating those patients prone to nausea and vomiting. This is because, as is explained in the Example below, (-)-tramadol is believed to modulate the emetic properties of (+)-tramadol, thereby reducing the overall emetic capability of racemic tramadol. This effect can be exploited for maximum benefit using different release profiles for the different enantiomers, as is discussed below.

The present invention is also believed to be particularly suited to the treatment of patients exhibiting abnormal CYP2D6 liver enzyme activity. The CYP2D6 gene encoding sparteine oxygenase is highly polymorphic, and an ever-increasing number of mutations are being identified. The wild-type gene is CYP2D6*1A. Any person not having the wild-type gene can be categorised as exhibiting abnormal enzyme activity. The precise nature of any particular mutation determines the degree to which a patient exhibits abnormal enzyme activity. Thus, by applying simple laboratory genetic analysis techniques it is possible to ascertain the approximate rate at which (+)-tramadol will be metabolised by a particular patient, and therefore how rapid and effective analgesia will be.

In accordance with the present invention it is envisaged that patients phenotypically or genotypically diagnosed as extensive metabolizers of racemic tramadol will particularly benefit from administration of non-racemic tramadol, since they are especially prone to side-effects such as nausea and vomiting. Furthermore, the administration regime may be tailored to suit any individual patient once his or her CYP2D6 genotype is known.

Other non-racemic ratios of the two tramadol enantiomers are also useful in the treatment or prevention of pain, depending upon the cause of the pain and/or the patient to be treated. For instance, mixtures comprising a very high proportion of (-)-tramadol may be used, for example weight ratios in the range 0-10:100-90 (+:-), with patients particularly disposed to side effects associated with racemic tramadol. Another option is to employ a more even balance of the two enantiomers, with the more efficacious (+)-enantiomer in excess, for instance weight ratios in the range 60-80:40-20 (+:-), typically 60-70:40-30 (+:-). Such ratios may be useful in treating patients not particularly disposed to side effects associated with racemic tramadol, or where analgesic efficacy is of primary importance. Administration of (-)-tramadol before or at a faster rate than (+)-tramadol would, however, still be beneficial in reducing side effects.

In the context of the present Application, all quoted weight ratios should be interpreted as including a tolerance of, say, ± 5 wt.%.

The present invention is also believed to be particularly useful in the treatment of the pain and/or other effects associated with migraine. To this end, a further aspect of the present invention is the use of a non-racemic mixture of the single enantiomers of tramadol in the manufacture of a medicament for the prevention or treatment of migraine.

The amount of non-racemic tramadol administered to any particular patient will depend upon the patient and the conditions for which the non-racemic tramadol is administered, and on whether non-racemic tramadol is to be used in prophylaxis or in therapy. Suitable amounts for administration are readily derivable by the skilled person.

The different enantiomers of tramadol may be administered simultaneously, separately or sequentially. They may be formulated for either immediate or controlled release, or a combination of the two, or for release at different rates, or at different times. Preferred modes of administration release (-)-tramadol before or at a faster rate than (+)-tramadol, so as to optimise the effect of (-)-tramadol on the emetic properties of (+)-tramadol. Although, situations may be envisaged, where the reverse may be required, and it is desired to administer (+)-tramadol before or at a faster rate than (-)-tramadol.

A particularly preferred mode of administration is with (-)-tramadol in immediate release form and (+)-tramadol in controlled release form, by employing a combination of immediate and controlled release technologies, as described in WO-A-9840053, the contents of which are incorporated herein by way of reference. It is envisaged that a dosage form of this type may be particularly beneficial in achieving rapid analgesia without the concomitant side effects associated with administration of racemic tramadol.

A number of different types of dosage form can be envisaged for the non-racemic mixtures of the present invention, for administration by a variety of routes, e.g. oral, rectal, transdermal, nasal, ophthalmic, pulmonary and injectable (subcutaneous or intravenous). Suitable dosage forms include, for example, tablets, suppositories, capsules, e.g. containing multiparticulates, patches, polymer implants, aerosols, liposomes or microparticulates for injection, and any other conventional dosage form.

Particularly preferred dosage forms are described in WO-A-9840053. Of the dosage forms described in that document, a bilayered tablet is particularly preferred, including (-)-tramadol for immediate release in one layer and (+)-tramadol for controlled release in another layer.

The results upon which the present invention are based are reported in the following Example.

Example

The objective was to identify the optimal range of enantiomeric ratios capable of providing the most beneficial therapeutic index, in terms of both analgesic efficacy and reduction of the nausea and vomiting associated with racemic tramadol.

Two studies were carried out to determine analgesic efficacy and emesis of tramadol and its enantiomers in the rat and the ferret, respectively. Comparison of the data obtained in these studies enabled determination of a range of optimal enantiomeric ratios for these species. Pharmacokinetic/ pharmacodynamic modelling allowed this data to be extrapolated to humans.

Assessment of Analgesic Efficacy

Tramadol and its pure enantiomers were examined for their analgesic efficacy in the rat using the Randall-Selitto test (Arch. Int. Pharmacodyn. (1957) 111:409-419) in the rat. This test was designed to measure the effect of tramadol and its enantiomers on yeast-induced analgesia, with pain perception being assessed by an increased by increase in pressure to the paw using an analgesy meter. For comparative purposes the effects of the active metabolites of the tramadol enantiomers, O-desmethyiltramadol, were also tested.

Different amounts of each of the test substances were orally administered to rats, using a constant dose volume of 10 ml/kg. Immediately following administration, 0.1 ml of a 20% w/v suspension of Brewer's yeast in saline was injected subcutaneously into the plantar surface of the right hand paw of each rat to induce hyper-algesia. The

left hind paw was similarly injected with 0.1 ml saline, as a control.

Measurements of pressure tolerated were taken from the left (non-inflamed) and right (inflamed) paws 30 minutes
5 after administration of the test substance.

The results observed are illustrated in Figure 1, for the inflamed paw, and Figure 2, for the non-inflamed paw, as a percentage increase in pain tolerance with varying doses of test substance. In both Figures, T = tramadol and
10 M1 = O-desmethyltramadol.

Assessment of Nausea

Tramadol and its pure enantiomers were examined for their nauseous effects in the ferret. For comparative purposes the effects of the active metabolite of (+)-
15 tramadol, (+)-O-desmethyltramadol ((+)-M1), were also tested. Orally-dosed ferrets were observed over a period of 4 hours for signs of retching and vomiting. Any ferret that retched or vomited over the 4-hour period was regarded as a responder, i.e. as exhibiting nausea.

20 The results are illustrated in Figure 3; T and M1 represent tramadol and O-desmethyltramadol, as in Figures 1 and 2. As expected, (+)-M1 is highly emetic. (-)-tramadol is seen to be non-emetic at doses of up to 200 mg/kg. In comparison, (+)-tramadol induces nausea in 75% of ferrets
25 at 50 mg/kg, while the racemate causes nausea in 25% of animals at 100 mg/kg. Although the racemate is a 50:50 mixture of the two enantiomers it is seen to induce less nausea than would be expected based on its content of (+)-enantiomer. This disparity can be explained by the ability
30 of the (-)-enantiomer to modulate emesis associated with the (+)-enantiomer.

Bioanalysis of plasma samples and liver microsome analysis have shown that tramadol is metabolised similarly in the rat, the ferret and the human. It is therefore
35 possible to compare the data obtained in each of these studies, to arrive at the optimal range of enantiomeric ratios for these species. Furthermore, by pharmacokinetic/

pharmacodynamic modelling techniques, it is possible to extrapolate the data obtained to humans, to arrive at the optimal range of enantiomeric ratios for use in the present invention.

5

Claims

1. A product comprising a non-racemic mixture of the single enantiomers of tramadol as a combined preparation (kit) for simultaneous, separate or sequential use in the treatment or prevention of pain, the mixture comprising at least some (-)-tramadol.
2. A product according to claim 1, which comprises at least 60% by weight (-)-tramadol.
3. A product according to claim 2 in which the single enantiomers are in a weight ratio of 10-40:90-60 (+:-).
4. A product according to claim 2 in which the single enantiomers are in a weight ratio of 20-40:80-60 (+:-).
5. A product according to claim 2 in which the single enantiomers are in a weight ratio of 0-20:100-80 (+:-).
6. A product according to any preceding claim, which releases the (-)-enantiomer before the (+)-enantiomer.
7. A product according to any of claims 1 to 5, which releases the (-)-enantiomer faster than the (+)-enantiomer.
8. A product according to any of claims 1 to 5, wherein the (-)-enantiomer is in immediate release form and the (+)-enantiomer is in controlled release form.
9. Use of a non-racemic mixture as defined in any of claims 1 to 5 in the manufacture of a medicament for the treatment or prevention of pain.
10. Use according to claim 9, wherein the pain is pain associated with migraine.

11. Use according to claim 9, which is for the treatment of a patient disposed to side effects associated with administration of racemic tramadol.
- 5 12. Use according to claim 11, wherein the side effects are selected from nausea, vomiting, dizziness, constipation, sedation, blurred vision, drowsiness, somnolence, hallucinations, respiratory depression, and emporia, especially nausea and vomiting.
- 10 13. Use according to claim 9, which is for the treatment of a exhibiting abnormal CYP2D6 liver enzyme activity.
- 15 14. Use of a non-racemic mixture as defined in any of claims 1 to 5 in the manufacture of a medicament for the for the treatment or prevention of migraine.
- 20 15. A product comprising a non-racemic mixture as defined in any of claims 1 to 5, and a pharmaceutically-acceptable carrier.
16. A product according to claim 15, which releases the (-)-enantiomer before the (+)-enantiomer.
- 25 17. A product according to claim 15, which releases the (-)-enantiomer faster than the (+)-enantiomer.
- 30 18. A product according to claim 15, wherein the (-)-enantiomer is in immediate release form and the (+)-enantiomer is in controlled release form.
19. A product according to any of claims 15 to 18, which comprises the two enantiomers in separate portions thereof.
- 35 20. A product according to claim 19, which is a bilayered tablet comprising (-)-tramadol in one portion thereof, and (+)-tramadol in another, separate, portion thereof.

1/2

Figure 1

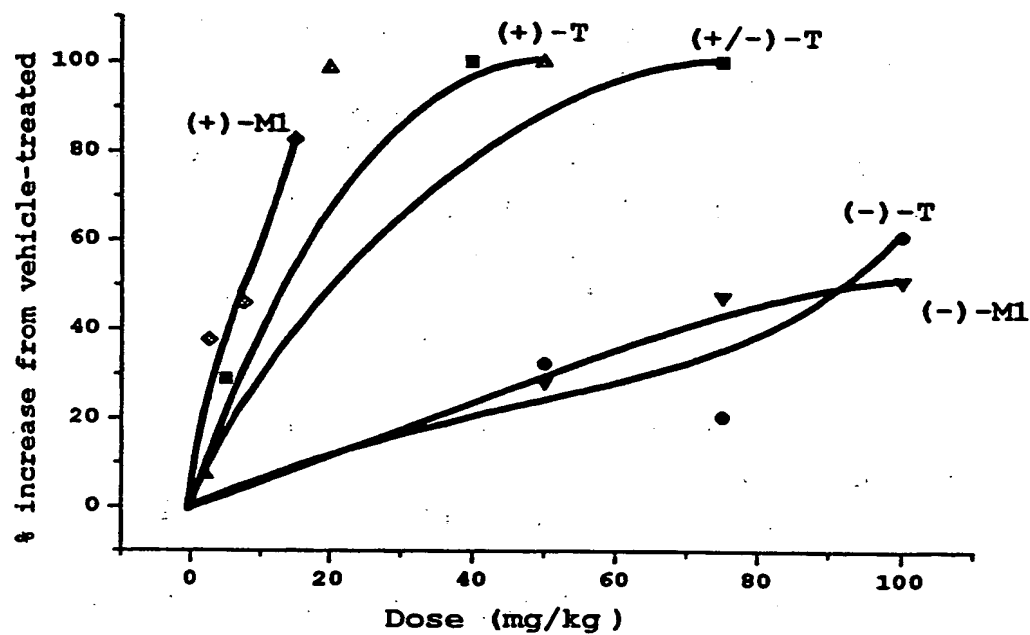
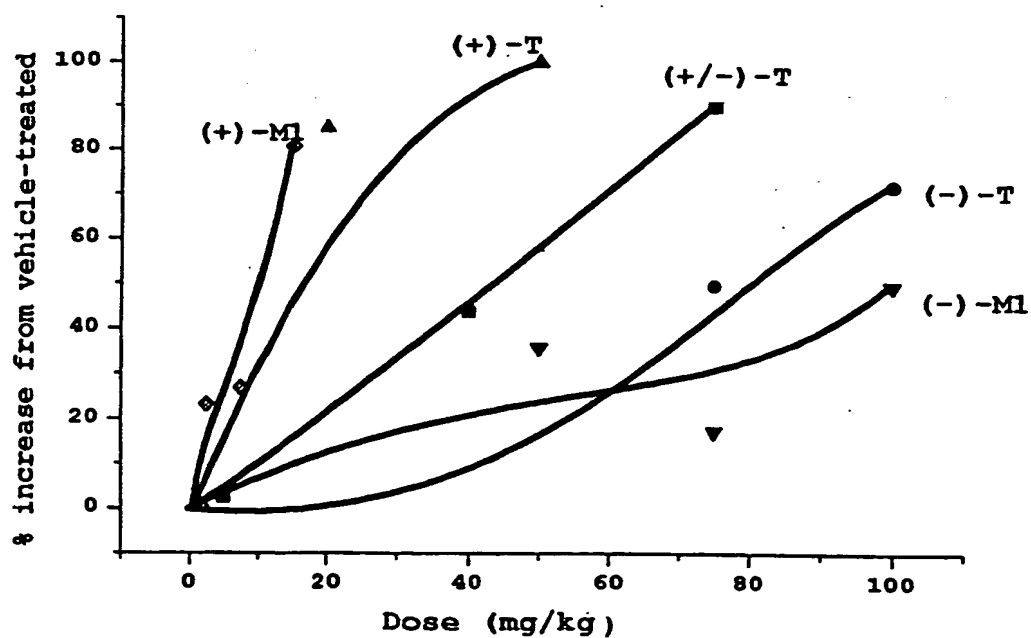
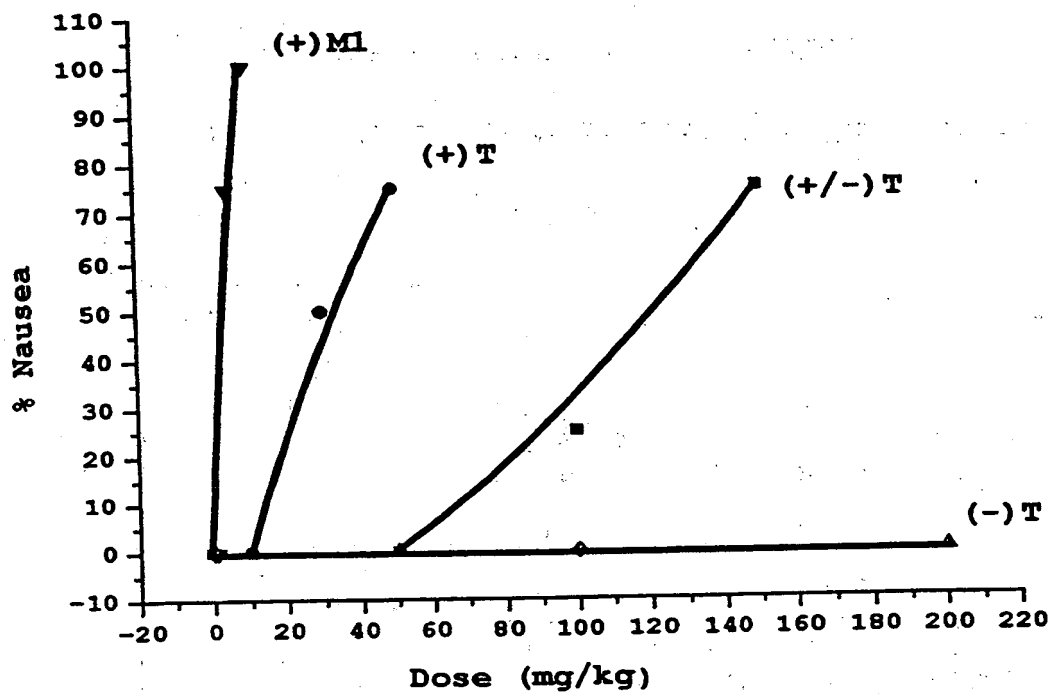


Figure 2



SUBSTITUTE SHEET (RULE 26)

Figure 3



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/04021

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/74 A61K31/135 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, L	<p>WO 98 40053 A (BARDSLEY HAZEL JUDITH ; DARWIN DISCOVERY LTD (GB); GILBERT JULIAN C) 17 September 1998 (1998-09-17) cited in the application</p> <p>Document which may throw doubt on the priority claim</p> <p>page 1, line 25 - line 31; claims 1,5,8,13,15,18,26,28-30; examples</p> <p>page 2, line 10 -page 3, line 12</p> <p>page 4, line 15 -page 5, line 9</p> <p>page 6, line 30 -page 7, line 2</p> <p style="text-align: center;">-/--</p>	<p>1,2,5-9, 11,12, 15-20</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 April 2000

Date of mailing of the international search report

27/04/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/04021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FRANKUS E ET AL: "UEBER DIE ISOMERENTRENNUNG, STRUKTURAUFKLAERUNG UND PHARMAKOLOGISCHE CHARAKTERISIERUNG VON 1-(M-METHOXYPHENYL)-2-(DIMETHYLAMINOMETHYL)-CYCLOHEXAN-1-OL. ON SEPARATION OF ISOMERS, STRUCTURAL ELUCIDATION AND PHARMACOLOGICAL CHARACTERIZATION OF 1-(M-METHOXYPHENYL)-2-(DIMETHYLAMINOMETHYL)-CYCLOHEXAN-" ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH, vol. 28, no. 1A, 1 January 1978 (1978-01-01), pages 114-121, XP000644506 ISSN: 0004-4172 page 115, column 2, paragraph 2 - paragraph 3; table 6 page 120, column 2, paragraph 1</p>	1,2,5,9, 15
A	<p>POULSEN L ET AL: "THE HYPOALGESIC EFFECT OF TRAMADOL IN RELATION TO CYP2D6" CLINICAL PHARMACOLOGY & THERAPEUTICS, US, ST LOUIS, MO, vol. 60, no. 6, 1 December 1996 (1996-12-01), pages 636-644, XP000891863 page 367, column 2, paragraph 2 - last paragraph page 6387, column 1, paragraph 2 page 641, column 2, paragraph 2 page 642, column 1, line 3 - line 11 page 642, column 2, line 7 - line 14</p>	9,13
A	<p>US 5 204 116 A (EDGREN DAVID E ET AL) 20 April 1993 (1993-04-20) page 2, line 48 - line 53; claims 1,4; figures 1-3</p>	20
X,P	<p>WO 99 42095 A (ASTA MEDICA AG) 26 August 1999 (1999-08-26) page 1, line 1 - line 9 page 7, line 25 - line 28; claim 1</p>	1,5,9, 10,14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/04021

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/04021

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9840053 A	17-09-1998	AU 6508998 A EP 0969818 A NO 994412 A	29-09-1998 12-01-2000 20-10-1999
US 5204116 A	20-04-1993	US 5338550 A	16-08-1994
WO 9942095 A	26-08-1999	DE 19807535 A AU 3514899 A	26-08-1999 06-09-1999